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p21 as an essential regulator of neurogenic homeostasis in neuropathological conditions

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Adult neurogenesis is a highly dynamic process that leads to the production of new neurons from a population of quiescent neural stem cells (NSCs). In response to specific endogenous and/or external stimuli, NSCs enter a state of mitotic activation, initiating proliferation and differentiation pathways. Throughout this process, NSCs give rise to neural progenitors, which undergo multiple replicative and differentiative steps, each governed by precise molecular pathways that coordinate cellular changes and signals from the surrounding neurogenic niche. The ultimate goal of this complex genetic machinery is to ensure a continuous supply of new, mature, and functionally active neurons to pre-existing neural circuits, while also maintaining the neural stem cell pool as intact as possible, both under physiological conditions and in response to positive or negative external stimuli (Niklison-Chirou et al., 2020). In fact, disruption of this delicate balance can lead to neurogenic deficits or depletion of the NSC pool. In this context, p21 has been identified as a key regulator of two pivotal processes in adult neurogenesis: the transition between quiescence and activation of NSCs, and the progression of progenitor proliferation (Maeda et al. 2023).

Two recent works have highlighted additional roles of p21 expression in regulating adult hippocampal neurogenesis in neuropathological conditions (**Figure 1**). Chiani et al. (2024) demonstrated that p21 played a crucial role in coordinating the hippocampal neurogenic response in a post-injury context by maintaining the integrity of the NSCs pool, while Wang et al. (2024) have emphasized how this gene, by interacting with oxidative stress-associated gene, was able to mediate the effect of corticosterone (CORT) on the hippocampal neurogenesis deficits.

In the first study, the authors used a new murine model of conditional deletion of p21 in NSCs, while in the other p21 was overexpressed through adenoviral infection of the DG. Both studies converge on the importance of this gene in regulating the homeostasis of neurogenic processes in neuropathological conditions. Furthermore, these papers significantly broaden the overall understanding of p21 as an essential gene for regulating both the proliferative steps of NSCs and the differentiation dynamics of NSCs and neuroblasts, intimately interacting with the molecular pathways that orchestrate the cell cycle. Indeed, in the work of Chiani et al. (2024), the authors observe that, under physiological conditions, the conditional deletion of p21 in NSCs following Tamoxifen administration induces an increase in the recruitment of quiescent NSCs into the cell cycle. This event, in turn, enhances proliferative and differentiative processes within the hippocampal neurogenic niche leading to a massive increase in adult neurogenesis and to an improvement of mnemonic tasks dependent on hippocampal neurogenesis. This event is most likely due to an upregulation of key players of the cell cycle, such as cyclin D2, involved in the positive mitotic progression of NSCs. Supporting this hypothesis, a study has demonstrated that the over-expression of the protein complex cyclin D1/CDK4 induces a profound pro-neurogenic effect in the murine Dentate Gyrus (Artegiani et al., 2011). Another important aspect to consider is that the increased proliferation of p21-depleted NSCs does not involve replicative stress processes typically induced by hyper-proliferation, as observed in postnatal p21 KO mice, where a rapid depletion of the pool of hyper-proliferating NSCs occurs (Kippin et al., 2005). In fact, within postnatal neurogenic niches, the proliferative processes of NSCs and neural progenitors are characterized by a shorter cell cycle and a slower exit from the cycle compared to what is observed in adult neurogenic niches. Consequently, the p21 deletion during the post-natal period leads to a higher proliferative rate leading to replicative stress mechanisms followed by rapid depletion of the pool.

Chiani et al. (2024) demonstrated that in the adult hippocampus an exhaustion of the pro-neurogenic processes due to p21 depletion only 100 days after Tamoxifen administration. More importantly, no long-term depletion process of the NSC pool was observed. Indeed, the expression of p21 in adult NSCs may appear redundant, or even negative for the neuroplastic potential of adult hippocampal neurogenesis, a kind of "handbrake" that limits the source of adult NSCs within the DG. However, observations made in a post-injury context clearly suggest that the expression of this gene is essential for regulating the neurogenic steps following brain damage (Chiani et al., 2024). In fact, it is known that a mild/moderate traumatic brain injury (TBI) can stimulate hippocampal neurogenic processes as part of the broader neuro-reparative response that is established in the brain following cortical damage (Marzano et al. 2022). But what happens instead in the absence of p21 in NSCs following TBI? Chiani and collaborators addressed this question by demonstrating that an initial powerful increase in the activation and proliferation processes of NSCs is followed by a rapid and dramatic depletion of the pool that leads to a long-term impairment of adult neurogenesis and hippocampal-dependent mnemonic skills. These events lead us to make two general considerations. The first one is that the expression of p21 is not essential under physiological conditions, but rather when an external pro-neurogenic stimulus drives an increase in the activation and proliferation of quiescent NSCs. In these situations, p21 finely modulates the molecular pathways that orchestrate the progression of the various stages of the cell cycle, preventing excessive activation/proliferation of NSCs. This excessive proliferation leads to depletion of the NSC pool and impairment of neurogenesis. The second consideration arises from the hypothesis that within the hippocampal neurogenic niche, there is a common mechanism - likely involving p21 and other genes expressed during the cell cycle - capable of maintaining the activation/proliferation rate of NSCs below a certain threshold. If this threshold is exceeded, it leads to a progressive exhaustion of the NSC pool.

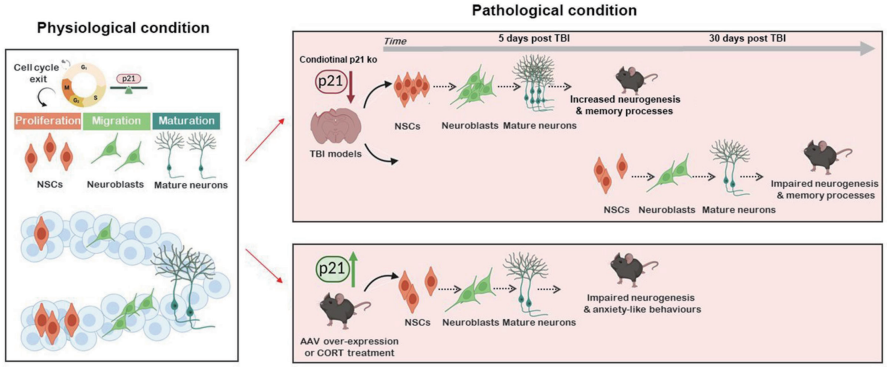

Figure 1 | **P21 modulation in pathological conditions alters hippocampal neurogenic processes.**
p21 plays a key role in regulating adult hippocampal neurogenesis by controlling the transition between quiescence and activation of NSCs and the proliferation of progenitors (left box). However, recent studies indicate p21 as a key homeostasis regulator of neurogenic response in neuropathological conditions (right box). Created with BioRender.com. AAV: Adeno-associated virus; CORT: corticosterone; NSCs: neural stem cells; TBI: traumatic brain injury.

It is as if a compromise has been reached in the hippocampal neurogenic niches, where, at the expense of slightly reduced neuroplasticity, the integrity of the NSC pool is preserved, ensuring the availability of potentially inducible NSCs in cases where a pro-neurogenic stimulus threatens the primary source of new hippocampal neurons.

Furthermore, a recent study elegantly describes how a moderate TBI induces a specific increase in neurogenesis at the expense of astrogliogenesis, originating from common neural precursors, the Radial Glial-like NSCs (Bielefeld et al. 2024). In this study, the Authors identified six differentiation stages of NSCs (N-stage 1–6), some of which (N-stage 1, 2, 4, and 5) are preferentially increased following TBI. Regarding the post-injury proliferative dynamics, the study characterized two main phenomena: (1) a significant increase in proliferation within the NSC-stage 2 population; (2) up-regulation of the pro-proliferative gene Ppp1r14b in RG-like NSCs, which plays a crucial role in the post-injury activation and proliferation of these cells. Although the involvement of cell cycle-regulating genes, such as p21 or cyclins, in cell fate dynamics and proliferation within NSCs is not mentioned, this study confirms that TBI induces a series of gene changes that modify the NSCs fate decision and transition rather than their developmental stages.

In the second work we considered, the new role attributed to the p21 gene in the hippocampal neurogenic niche is framed within a context characterized by phenomena associated with CORT-induced anxiety states (Wang et al. 2024). In this study, the authors discovered that chronic treatment with CORT induces an increase in the expression of p21 in the hippocampal dentate gyrus, which interacts with oxidative stress-related genes and mediates the negative impact of CORT on adult neurogenesis and hippocampus-mediated emotional responses. Confirmation of involvement of p21 in the CORT-mediated pathway comes from the overexpression of p21 in the DG that partially recapitulates some of the phenotypes induced by chronic exposure to CORT, including impairment of adult hippocampal neurogenesis, reactive oxygen species (ROS) accumulation, and anxiety-like behavior. Moreover, the finding that antioxidants partially mitigate p21 upregulation-induced hippocampal dysfunction and anxiety-like behaviors suggests a direct correlation between p21 over-expression and ROS accumulation. The molecular mechanisms underlying these interactions are still poorly understood, although it has been hypothesized that ROS accumulation following p21 up-regulation may be due to p21-induced mitochondrial impairment with a consequent generation of ROS through a sequential signaling cascade (Passos et al. 2010). Alternatively, it has been suggested that ROS-induced DNA damage results in p53 activation, which in turn up-regulates p21, creating a reinforcing feedback loop formed by p21-ROS-p53 (Liu et al. 2008). In conclusion, Wang et al. (2024) suggest that p21 represents a key modulator in hippocampal anxiety-related processes, capable of inducing cell cycle arrest and oxidative stress in response to elevated CORT levels.

While previous studies have hypothesized a regulatory role of p21 in hippocampal neurogenesis during inflammatory processes (Zonis et al. 2013) and in response to antidepressant treatment (Pechnick et al. 2011), these last two researches greatly expand the molecular and cellular landscape within which this gene contributes to maintaining a cellular balance essential for the correct functioning of hippocampal neurogenesis. As evidence of this hypothesis, modifications in p21 expression within the hippocampal neurogenic niche have profound effects not only on the proliferative and differentiative dynamics of newly generated NSCs and progenitor cells but also on hippocampal functionality, influencing learning, memory, and emotional behavior. Consequently, the identification of p21 as a hub gene in key hippocampal neurogenic pathways highlights the pivotal role of this gene in counteracting the anti-neurogenic effects of different neuropathologies, including mood disorders and brain injuries.

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